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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
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Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Composition of Antimicrobial Agent Useful in the Treatment of Acne and Candida

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 8 ☐ CD(s), Number _____

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☐ Application Date Sheet. See 37 CFR 1.76

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[Page 1 of 2]

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

A PROVISIONAL PATENT APPLICATION

FOR

Composition of Antimicrobial agent useful in the treatment of Acne and Candida

BACKGROUND OF THE INVENTION

About acne vulgaris infection

Acne is a multi-factorial disease that affects the sebaceous (oil-producing) hair follicles (pores) of the skin, primarily on the face and neck, but often on the back and chest as well, where hairs grow most densely. The current understanding of the disease is that increasing levels of androgen sex hormones at puberty lead to increased production of oils and epidermal cells lining the follicles. In its less severe forms, acne is characterized by non-inflammatory papules (comedones, whiteheads or blackheads), which are pores plugged by excessive sebum production and trapped skin cells. In more severe cases, patients develop inflammatory lesions, in which the common and generally non-pathogenic skin bacterium plays a significant role.

According to the American Academy of Dermatology, acne vulgaris affects nearly 100% of adolescents and nearly half of adults over 25 in the U.S. Various sources estimate that 15-40% of Americans seek medical treatment for acne by their mid-teens. Every year, five million prescriptions for oral antibiotics are dispensed for acne treatment in the U.S. Additionally, U.S. prescription and over-the-counter sales of topical acne treatments total approximately $1.1 billion per year.

Although not a serious threat to general health, acne is one of the most socially distressing skin conditions, especially for adolescents, who must deal with a disfiguring disease that erupts just when sexual maturity makes them most sensitive about their appearance. Moreover, severe acne can lead to permanent scarring of the skin that carries the social distress throughout adulthood.

About existing treatment regimens

The goal for acne treatment is to clear existing lesions and prevent new ones from occurring. Current topical treatments for acne include benzoyl peroxide, retinoids, salicylic acid and antibiotics such as erythromycin and clindamycin. Broad-spectrum oral antibiotics, retinoids and hormone treatments are also prescribed, although many of these treatments produce undesirable and even dangerous side effects. Topical antibiotics kill off and decrease the population of P. acnes within follicles, as well as reduce the ability of this organism to generate pro-inflammatory molecules.

An important issue in the use of topical antibiotics is the emergence of bacterial resistance and cross-resistance, which can also occur with repeated courses of systemic antibiotics. Therefore, a topical treatment that is effective against P. acnes and does not induce resistance would offer an attractive alternative to currently available topical acne products.

Fungal Infections

Fungal infections are widely distributed in animal species. The most common agents of fungal infections include various species of the Candida and Aspergillus, The incidence of fungal infections has undergone a significant increase, particularly in humans due to increasing number of patients having impaired immune systems, either as a result of medical therapy for transplant patients or diseases such as AIDS which compromise the immune system. Fungal disease, particularly when systemic, can be life threatening to patients having an impaired immune system or become a chronic diseases effecting patient quality of life.

A number of prior art pharmaceutical agents are commonly used for the treatment of fungal diseases. These materials include compounds such as amphotericin B (AMB), triazoles and flucytosin. AMB is the drug of choice for many systemic fungal infections due to its broad range of activity; however, it is harmful to the kidneys and must be administered intravenously. Many of the triazoles exhibit broad ranging activity and can be administered orally; however, many strains of fungi have become resistant to these materials. Consequently, there is a need for new drugs which are effective in eliminating fungus disease, but are of low toxicity to patients. Ideally, these materials should be simple to prepare, stable, and easy to administer.

As will be described in further detail herein below, the present invention is directed to a highly effective agent for controlling fungus disease. The composition described here is specifically prepared from available carbohydrate polymers such as chitin or chitosan (as describe below) and chelated with a naturally occurring broad spectrum antibacterial isolated initially from plant. These and other advantages of the present invention will be readily apparent from the discussion, description and examples which follow.

BRIEF SUMMARY OF THE INVENTION

In accordance with the present invention, water soluble composition of Co-polymer of N-acetylglucoseamine (AGA)-glucosamine (GA)-pyrithione (PR) having the empirical structural formula: $[(NAGA)_X (GA)_Y (PR)_Z]_N$ wherein x is 0.01-0.3, y is 0.3 to 0.98 and z 0.01 to 0.3 molar fractions having total x+y+z=1, and N has a value between about 1 and about 100 with a molecular weight range of 1K to 150K.

This compound is an excellent gel like substance and will form a film upon drying. Various medical crème formulations have been prepared and tested. A carbohydrate surfactant at 0.01 to 1% (Decyl Polyglucose, commercially available from Henkel Corp.) has been to enhance the formulation activity. The combination of a broad-spectrum pyrithione with carbohydrate co-polymer provide a delivery and active ingredient with superior antimicrobial activity again dermal pathogens like acne and candida. The long term stability of the complex make AGP potentially very useful pharmaceutical as an antimicrobial agent in a chronic dermatological diseases such as acne, yeast infections and other general dermatitis.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, AGP can be prepared first by manufacturing the co-polymer under control thermal and acid hydrolysis of purified chitin. The molecular sizing of the co-polymer can be achieved by either treatment with endo-chitinases (enzymatic treatment) or by either peroxide oxidation or reductive alkylation (chemical glycosidic hydrolysis). Again temperature and time are important to achieve the proper ratio of glucosamine and N-acetyl glucosamine the polymeric building block. The co-polymer can also produced by fractional control acetylation of polyglucosamine available commercially also as USP grade chitosan from various sources. The molecular weight of commercially available chitosan typically between about 200,000 and about 2,000,000 and is

over 95% deacetylated. Using this reactant, AGP is produced by three steps, acid hydrolysis, partial acetylation and chelation with pyrithione acid or salts. The chelation reaction is done with timely cycling of pH and temperature, finishing with neutral pH and room temperature. The average molecular weight of the resulting AGP is typically in the range of between about 2K and 120K, more typically in the range of between about 15,000 and about 80,000. Finally the formulation can be optimized with standard ingredients to make a gel, cream or a patch. A proffered surfactant is an alkyl polyglucose, added at 0.01 to 1%, which further enhance the formulation activity.

Sources of raw materials and manufacturing

AGP is prepared by control deacetylation of chitin [B-(1-4)-poly-N-acetyl-D-glucosamine], an abundant natural by-product of the crustacean process industries. It can also be produced from microbial biomass such as mushroom, fungi and yeast.

Pyrithione is commercially available as zinc, cupper or sodium pyrithione from ARCH Chemicals Inc. and they are registered under the trademark OMADINE. They are widely used as antibacterial and antifungal in the industrial, cosmetic and shampoo. However, because these pyrithione products are absorbed through the skin fairly rapidly, they may only be used at relatively low concentrations in products intended for topical application. They are also sensitive to oxidation and rapid photo degradation.

The proffered surfactant for the composition is an alkyl-polyglucose, which when added at 0.01 to 1% further enhance the formulation application and activity. Alkyl-polyglucose is available commercially from Henkel Corp.

The current invention stabilized chelated pyrithione in a complex carbohydrate based co-polymer that not only slow down pyrithione absorption into the skin, increase stability of pyrithione but also bind to the microorganisms, altered their membrane porosity (interfere with Ca ATP pumps) and increase susceptibility to the pyrithione. The emulsification property of the AGP provides better penetration to oily environment of Acne bacteria.

In preclinical evaluation the antibacterial activity against P. acnes and various pathogenic candida AGP showed excellent bactericidal activity also against resistant pathogenic strains.

Activity of AGP against P. acnes and other pathogens

Preliminary study indicate that the bacteria was completely inhibited by concentration at less than 0.1 mg/mL. Similarly AGP was active toward *Escherichia coli* and *Staphyloccocus aureus* at low concentration.

Case study with acne patients using 4% active AGP formula have shown remarkably results in less than 48 hours. The formula had no irritation or other side effect and could be also covered with make up.

Activity against Candida In-vitro and In-vivo

In vitro study with AGP against a wide spectrum of pathogenic yeast, including azole-resistant isolates. Over a dozen of pathogenic Candida have been tested and all were sensitive to the AGP with a minimum inhibitory concentration (MIC) ranged from 0.05 to 0.7 microgram per milliliter.

Pre-clinical study with three C. albicans isolates, including one fluconazole-resistant strain was performed with immunosuppressed animals with cyclophosphamide. Induced infection was treated with topical application of AGP for a period of 1-7 days. AGP at 0.25% was found to be equivalent in clearing the infection as 2% miconazole, and was free of local adverse effects.

PROCESSING OF CHITIN

Chitin is easily obtained from crab or shrimp shells and fungal mycelia. In the first case, chitin production is associated with food industries such as shrimp canning. In the second case, the production of chitosan-glucan complexes is associated with fermentation processes, similar to those for the production of citric acid from Aspergillus niger, Mucor rouxii, and Streptomyces, which involves alkali treatment yielding chitosan-glucan complexes. The alkali removes the protein and deacetylates chitin simultaneously. Depending on the alkali concentration some soluble glycans is removed. The processing of crustacean shells mainly involves the removal of proteins and the dissolution of calcium

carbonate that is present in crab shells in high concentrations. The resulting chitin is deacetylated in 40% sodium hydroxide at 120 oC for 1-3 h. This treatment produces 70% deacetylated chitosan.

Manufacturing Example:

Chelation of co-polymeris conveniently carried out by slurrying the carbohydrate co-polymer solutions with the desired chelation agents.

a. A slurry was prepared by stirring 1 g of prepared co-polymer (15:85, N-acetylglucosamine to glucosamine, MW 60Kd) thermally and chemically hydrolyzed chitin into 25 g DI water. PH was adjuted to 5 with lactic acid. A 50% solution of pyrithione acid (ARCH chem. Inc.) was added by mixing in 0.25 mL into the 25 mL solution. The mixture was mixed for 1 hour at 37C and the pH was increased with 1M NaOH to pH 5.5. A 0.1 g Decyl Polyglucose (50% solution) was added and slow mixing was continued for 30 minutes.

b. A slurry was prepared by stirring 1 g of prepared co-polymer (15:85, N-acetylglucosamine to glucosamine, MW 60Kd) thermally and chemically hydrolyzed chitin into 25 g DI water. PH was adjuted to 5.0 with gluconic acid. A sodium OMADINE® solution (a 40% solution of sodium pyrithione, ARCH Chem. Inc.) at 0.5 mL was added and stirring continue for 1 hour. at 37C and the pH was increased with 1M NaOH to pH 5.5. A 0.1 g Decyl Polyglucose (50% solution) was added and slow mixing was continued for 30 minutes.

c. A slurry was prepared by stirring 1 g of prepared co-polymer (15:85, N-acetylglucosamine to glucosamine, MW 40 Kd) thermally and hydrogen peroxide hydrolyzed chitin into 25 g DI water. PH was adjuted to 5.0 with gluconic acid. A Zinc OMADINE® slurry (a 40% slurry solution of Zinc pyrithione, ARCH Chem. Inc.) at 0.5 mL was added and stirring continue for 1 hour at 37C and the pH was slowly increased with 1M NaOH to pH 5.5. A 0.1 g Decyl Polyglucose (50% solution) was added and slow mixing was continued for 30 minutes.

The durability of the these co-polymer complexes was determined by subjecting these complexes to typical end-use conditions such as would be expected of a over the counter device and dermal preparation. A 4% solution has been found stable and active after 4 years of storage at room temperature.

MIC Results for AGP on variety of candida pathogenic isolate

Drug concentration are in g/ml

Candida	AGP-2.3/0.8	AGP – 4/0.8	AGP-4/1.6	AGP-4-2.4
AIbicans 90028	0.078	0.156	0.078	0.078
3153A	0.156		0.078	0.078
36802	0.078			
Fluconazole				
resistant				
Albicans.-				
DT 1413A	0.312			
MF 390	0.312			
DT 492	0.312			
DT 740	0.312			
SZ	0.312			
DT 01-A	0.312			
LF 392.95	0.312			
LF 412.95	0.312			
JH 488	0.312			
DT 1167 A	0.312			
MF-109	0.156			
LF 360.95	0.612			
Glabrata	0.312	1.25	2.5	2.5
32554				
X-62431	0.312	0.625	5	5
90030	0.625		10	5
MF 028	0.156			
MF 037B	0.312			
RI 422	0.078			
MF 057	0.625			
Parapsilosis	0.625		5	2.5
22019				
90018	0.078		0.078	0.037
Tropicalis	0.156			
44508				
JH 782	0.312			
JH 545A	0.312			
JH 491A	0.156			
JH 780B	0.312			
Krusei 6428	0.312			
RI 1202	0.078	0.156	0.078	0.078
824A	0.625	2.5	5	2.5
JH 568	2.5			
Trichomonas	2.5-5			

ABSTRACT OF THE DISCLOSURE

In accordance with the present invention, a water-soluble chelated complex of a co-polymer of acetylglucosamine-glucosamine pyrithione salt (AGP), has been produced. This composition is characterized by a highly viscose texture with excellent surface properties and extremely long acting antimicrobial activity. The antimicrobial activity against acne bacteria has been found superior to the benzyl peroxide the leading acne medication. In addition the AGP has been proven to be effective against many pathogenic yeast. The AGP has the potential to be useful as long acting broad-spectrum antimicrobial composition in a variety of dermatological medicaments and cosmetics .

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